Keratoacanthoma centrifugum marginatum: A diagnostic and therapeutic challenge

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INTRODUCTION

Keratoacanthoma centrifugum marginatum (KCM) is a rare variant of keratoacanthoma (KA) possessing several characteristics distinguishing it from typical KAs. Clinical presentation deviates from common KAs with lesions that continually expand peripherally.[1-3] KCM also deviates from the usual histologic findings with a lack of some classic KA features. This is probably attributable to sampling issues given the size of the lesions and the limited capacity of a biopsy. Because of its rarity and lack of distinctive histopathologic features, KCM poses a difficult diagnostic challenge to clinicians and pathologists. Excellent communication and collaboration between the clinician and the pathologist is crucial for the correct and timely diagnosis, allowing for quick and proper treatment of the patient.

Abbreviations used:

KA: keratoacanthoma
KCM: keratoacanthoma centrifugum marginatum

CASE PRESENTATION

We report a case of a 71-year-old white woman with a single large erythematous tumor on her left anterior knee. Originally, the lesion began as a single erythematous papule after local trauma. She reports the tumor expanded to an irregular 7.5- × 3.5-cm arciform, nonblanchable erythematous plaque with hyperkeratotic papulonodular borders over approximately 1 year (Fig 1).

An initial shave biopsy found irregular psoriasiform epidermal hyperplasia with squamous atypia. The differential diagnosis consisted of unusual psoriasis on stasis altered skin, pseudocarcinomatous epidermal hyperplasia in the setting of an inflammatory process, infection, or perforating disorder; KCM; and squamous cell carcinoma. Another biopsy a few weeks later histopathologically showed epidermal hyperplasia again, this time with a dense mixed inflammatory infiltrate, and without a dermal neoplasm or infectious organisms identified. Concurrent bacterial, fungal, and mycobacterial cultures returned negative. As a result, the patient was treated with multiple rounds of topical steroids without improvement. She also received 3 courses of trimethoprim/sulfamethoxazole and 1 course of doxycycline, each lasting approximately 10 days, without any appreciable effect on the tumor. Ultimately, a large incisional biopsy found zonal changes from the periphery to the center of the lesion. The outer lesion margin exhibited pseudoepitheliomatous hyperplasia with underlying islands of glassy, eosinophilic keratinocytes with squamous pearls and minimal atypia in the dermal component. Toward the center of the lesion were fibrosis and a lack of epidermal hyperplasia (Figs 2 and 3). In the dermis, both superficially and deep, was a mixed infiltrate of lymphocytes, histiocytes, eosinophils, neutrophils, and numerous plasma cells (Fig 4).

Again, no organisms were identified after fungal, mycobacterial, and spirochete stains were performed. Again, concurrent cultures returned

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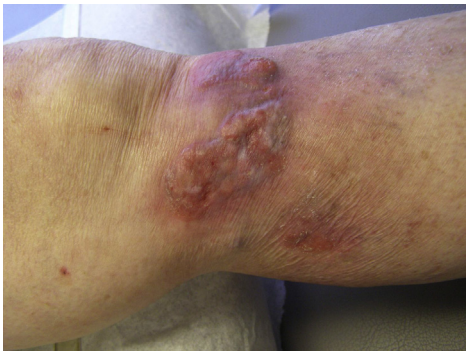

Fig 1. Keratoacanthoma centrifugum marginatum. The lesion began as a single erythematous papule that progressed to an irregular 7.5- × 3.5-cm boggy tumor on the left anterior knee approximately 1 year after localized trauma.

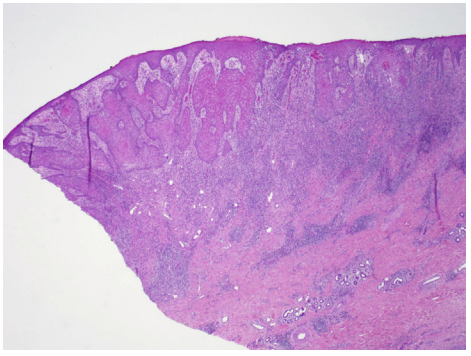

Fig 2. A low-power view of the incisional biopsy with zonal changes from the periphery to the center of the lesion. The outer edge is characterized by pseudoepitheliomatous hyperplasia and a dense mixed inflammatory infiltrate both superficially as well as deep. Centrally, the lesion shows fibrosis and a lack of epidermal hyperplasia. (Hematoxylin-eosin stain; original magnification: ×2.)

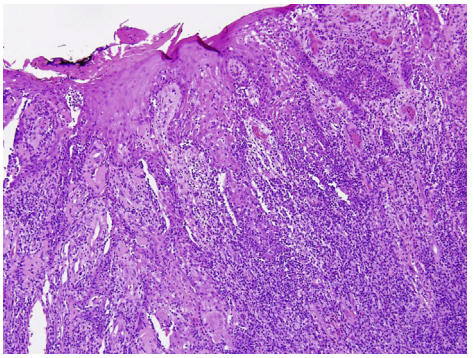

Fig 3. A high-power view shows islands of keratinocytes with squamous pearls and minimal atypia underlying pseudoepitheliomatous hyperplasia. (Hematoxylin-eosin stain; original magnification: ×20.)

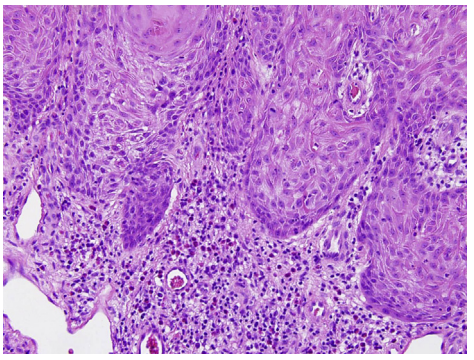

Fig 4. A high-power view shows the eosinophilic, glassy cytoplasm of the keratinocytes, minimal atypia, and a single mitotic figure near the basal layer. The dermal inflammatory infiltrate is a mixture of lymphocytes, histiocytes, eosinophils, and a few plasma cells. (Hematoxylin-eosin stain; original magnification: ×40.)

negative, except for mild growth of *Staphylococcus aureus*, corresponding to her superimposed infection. This lesion was diagnosed as compatible with KCM. Because the lesion was too large to excise entirely, the patient was treated with 2 courses of intralesional 5% 5-fluorouracil injectable solution. Each course consisted of 0.6 mL divided into 3 aliquots within the tumor mass, without precedent lidocaine. The 2 treatments were separated by 3 weeks. The patient had no adverse events other than discomfort at the time of injection. Treatment resulted in complete clinical clearance of the lesion within weeks (Fig 5). Follow-up at 2 years from definitive diagnosis showed no evidence of recurrence and no new lesions.

DISCUSSION

KAs are rapidly evolving tumors, composed of keratinizing squamous cells arising from the follicular infundibular epithelium. These lesions are purported to resolve spontaneously if left untreated.[1-4] KAs typically occur on sun-exposed skin in men past their fifth decade of life.[1,2] They usually present as firm, rounded, flesh-colored to red papules with a keratin-filled central crater.[1,3] These lesions are usually solitary but can be multiple.[4] Three stages characterize the growth course: initial rapid growth, maturation, and spontaneous involution, with each lasting 2 to 6 weeks.[2,4] Of the solitary forms, rare variants have been described to include subungual type, intraoral and mucous membrane type, giant KA, and marginated or centrifugum type (also called KCM).[3]

KCM was first described by Miedzinski and Kozakiewicz in 1962[5] and designated as a separate entity in 1965 by Belisario.[6] Its etiology is unclear but appears to be multifactorial, including chronic ultraviolet light exposure, smoking, and exposure to chemical carcinogens.[1] Unlike traditional KAs,

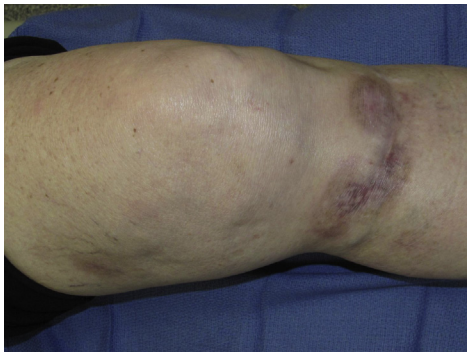

Fig 5. Clinical photo shows complete response within weeks of receiving 2 courses of intralesional 5-fluorouracil injections.

which have been reported to occur after trauma, to our knowledge, there are currently no reported cases of KCM associated with a solitary traumatic event.[7,8] Our patient's lesion, however, was noted to first occur after trauma to this local area. KCM is characterized by large lesions with progressive peripheral extension, reaching up to 20 cm; raised, rolled borders; and concomitant central healing leading to atrophy.[1-3] Unlike classic KAs, however, KCM does not show a tendency for spontaneous regression.[1] Although locally disfiguring, the general belief is that KCM is a benign entity, as no cases, to our knowledge, have been reported to metastasize.[1]

Histopathologically, KCMs can look similar to several other lesions. KCMs exhibit epidermal hyperplasia, which may appear pseudoepitheliomatous with hyperkeratosis. There is often a dense superficial and deep dermal mixed inflammatory infiltrate. Cytologically, the keratinocytes appear eosinophilic with glassy cytoplasm and minimal number of mitoses.[2,3] Thus, the differential diagnosis may include an infectious etiology, specifically, fungus or atypical mycobacterial, halogenoderma, hypertrophic lupus erythematosus, giant KA, and squamous cell carcinoma.[1-3,9] With such a broad differential diagnostic list, a lesion usually too large to perform an excisional biopsy, and histologic features that overlap those of many other lesions, KCM requires an index of suspicion on both the clinician's and pathologist's part.

Typically, surgical intervention is the preferred therapy for solitary KAs; however, because of the size of the lesions of KCM, this is not usually the most feasible therapy. There are reports of KCM being treated with oral retinoids with variability in success.[3] Additionally, topical 5-fluorouracil, intralesional injection of methotrexate, interferon alfa, or bleomycin as well as Mohs surgery have successfully been used, but no consensus regimens have been established.[1,4,9,10] No KCM lesions, to our knowledge, have been successfully treated with intralesional 5-flurouracil injection until our case, with complete response and regression of the tumor.

CONCLUSION

KCM is a rare variant of KA, with its diagnosis complicated by its rarity and lack of distinctive histopathologic features. Although trauma has been implicated as an etiologic factor in typical KAs, this is the first report, to our knowledge, that associates KCM with a traumatic event. Additionally, we present the first successful treatment of KCM with intralesional 5-fluorouracil injection.

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